## REMARKS

Claims 1-9 and 11-13 remain in the application. Only Claim 1 is in independent form.

Applicants acknowledge that the previous objection to Claims 3-5 and 9-13 has been withdrawn. Applicants further acknowledge that the rejection of Claim 4 under 35 U.S.C. §112 has also been withdrawn. Applicants also acknowledge that the rejection of Claims 1-3 and 5-8 under 35 U.S.C. §102 over Claremon, Gilligan et al., and Quaglia et al. have been withdrawn pursuant to Applicants' prior amendment and response.

The outstanding Office Action sets forth a rejection of Claims 1-13 under 35 U.S.C. §103 over Gilligan et al. and Gyermek. Applicants presume that the rejection applies to Claims 1-9 and 11-13 as Claim 10 was previously cancelled.

It is stated in the outstanding Office Action that Gilligan et al. disclose the compounds of the present invention "when its R2 is an alkyl group substituted by a phenyl. The reference clearly teaches that the tetralins are ligands for serotonin receptors. See page 365 after the fig. 14." It is further stated in the Office Action the Gyermek reference "clearly teaches that serotonin is widely distributed in the body within the central and peripheral nervous systems. It also teaches that serotonin inhibitors can also treat pain syndromes. (See page 402 of the reference). Thus one of skill in the art would have found it obvious use the compounds that that have serotonin activity to treat pain, especially ones that were associated with the nervous system, such as neuropathy, trigeminal neuropathy, migraine and such." The Office Action also discusses the reference to Goadsby which is cited for its alleged teaching of the relationship between migraine and peripheral trigeminal nerve activation.

The Gilligan et al. reference discloses tetralins which are stated to have good affinity for 5-$HT_2$ receptors and which are related to DuP 734, a 5-$HT_2$ antagonist. 5-$HT_2$ binding activity was tested by displacement of ketanserin, a known 5-$HT_2$ (5-$HT_{2A}$) antagonist (see the attached Kalkman reference).

The Gyermek reference discloses that 5-$HT_2$ antagonists are useful in the treatment of vascular disorders. It is also stated that "Serotonin reuptake inhibitors are of particular clinical importance in the treatment of psychological illnesses. Future use of these drugs is also envisioned in the treatment of certain types of pain syndromes." Applicants respectfully submit that the proper interpretation of the final sentence of that quotation relates to 5-$HT_2$ antagonists and further it seems clear from the context that the words "these drugs" relate only to serotonin reuptake inhibitors and not to the agonists and the antagonists of 5-HT receptors discussed in the same paragraph. In particular, it is stated that 5-$HT_1$ agonists are known to be useful in the treatment of a type of pain (migraine). Serotonin reuptake inhibitors are distinct from 5-$HT_2$ antagonists. Serotonin reuptake inhibitors increase the level of the neurotransmitter at the synapse by preventing (after release) the reuptake of serotonin back into the nerve terminals. On the other hand, 5-$HT_2$ receptor antagonists prevent 5-HT binding to this receptor and so prevent the downstream effects of receptor activation. Accordingly, it is therefore respectfully submitted that Gyermek makes no teaching or suggestion that 5-$HT_2$ antagonists are useful in the treatment of pain.

It is asserted in the Office Action that the Goadsby reference teaches the relationship between migraine and peripheral trigeminal nerve activation. However, Applicants respectfully submit that there is a distinction between trigeminal nerve activation, which occurs when triggered by, for example, dietary or visual factors, and trigeminal neuropathy, which occurs when there is injury or trauma to the nerve. Thus, there is no link between peripheral trigeminal nerve activation and trigeminal neuropathy. It is also stated in the Goadsby reference that "It has been suggested that the 5-$HT_2$ receptor may play a role in migraine prevention and this has been reviewed elsewhere," and cites to the Kalkman and Fozard et al. reference (a copy provided herewith).

The Fozard et al. reference states that "ketanserin, which has good selectivity for 5-$HT_2$ sites over 5-$HT_{1C}$ sites appears, at least in preliminary study, to be only weakly active as a migraine prophylactic agent" (p. 308). This is confirmed in the Kalkman reference, which states that "ketanserin [is] considered inactive as [a] migraine prophylactic agent" (p. 643).

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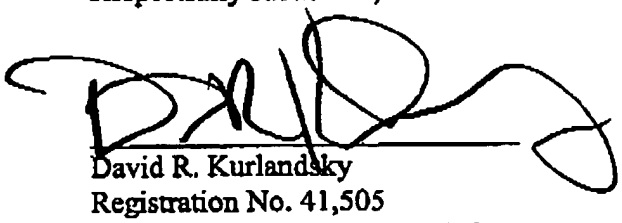
Kalkman further teaches that the classic 5-$HT_2$ receptor has been renamed 5-$HT_{2A}$ and that ketanserin is a selective 5-$HT_{2A}$ antagonist.

Accordingly, the prior art discussed above which forms the basis for the pending rejection of Claims 1-9 and 11-13 under 35 U.S.C. §103 teaches that the compounds disclosed in Gilligan et al. are 5-$HT_{2A}$ antagonists and that ketanserin, a known 5-$HT_{2A}$ antagonist is inactive as a migraine prophylactic agent. Thus, the prior art references provide no motivation for one of ordinary skill in the art to investigate the compounds disclosed in Gilligan et al. for utility in the treatment of pain, including migraine. Furthermore, Applicants have shown that the compounds of the present invention possess sodium channel antagonist activity, an entirely different target from the 5-$HT_{2A}$ receptor, and are thus suitable for the treatment of pain.

In view of the present amendment and foregoing remarks, reconsideration of the rejection and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any over payment in connection with this communication to our Deposit Account No. 23-0455.

Respectfully submitted,



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Attachments - Amended claims - Version with markings to show changes made
Kalkman, Life Sciences, 54:10, pp. 641-644 (1994)
Fozard and Gray, TIPS, 10, pp. 307-309 (1989)

## "VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claim 9 (twice amended). A method according to Claim 1 wherein pharmaceutical composition comprising a compound according to Claim 1 admixed with a pharmaceutically acceptable carrier[,] or diluent[, or carrier] therefor is administered to the mammal.